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PREPARATION OF INNUMERABLE EUTECTIC MIXTURES USING MIXED SOLVENCY CONCEPT

Simran Soni, Ashwinee Parihar, Ashutosh Rajak, Dharmendra Prajapati, Rajesh kumar Maheshwari,

Shri G.S. Institute of Technology and Science, 23, Park Road Indore-452003 Indore (M.P)

ABSTRACT:

The objective of this research is to use the mixed solvency concept to create an enumerable number of eutectic mixtures. We can replace hazardous organic solvents with eutectic mixtures. Physical and chemical properties influence the solubility of solutes. As per Maheshwari's mixed solvency concept, everything in the universe has the ability to dissolve each and everything, whether it is a gas, a liquid, or a solid. The concept of a eutectic mixture is "an isothermal, reversible reaction between two (or more) solid phases during the heating of a system, leading to the formation of a single liquid phase." To prepare for this study, we used a number of solutes and solvents.

KEYWORDS: Eutectic mixture**,** solubility, mixed solvency concept, solid as a solvent.

INTRODUCTION:

Eutectic mixture (1-5)

The eutectic mixture is defined as "an isothermal, reversible reaction between two (or more) solid phases during the heating of a system, as a result of which a single liquid phase is produced". The word eutectic is taken from the Greek word eutectos, which means low melting or easily fused. A eutectic mixture (EM) is defined as a mixture of two or more substances that, in a specific proportion, show a lower range of melting point and do not interact with each other to form a new chemical entity. Eutectic mixtures ought to be formulated in such a way that they ought to have major advantages in the pharmaceutical industry. Eutectic mixtures are the mixtures of active pharmaceutical ingredients and different portions of APIs and excipients, or a mixture of excipients and excipients. EM plays an important role in drug delivery. The essential parameters are hydrogen bond donor and hydrogen bond acceptor. With the help of eutectic mixtures, we can replace harmful organic solvents. EM can be employed for enhancement of drug solubility, bioavailability, as well as drug permeation through skin. This also has better biodegradability and biocompatibility.

Hydrotropic solubilisation

Hydrotropic solubilization refers to the improvement of a drug's aqueous solubility in the presence of a significant amount of a hydrotropic agent. Newberg (1916) coined the term "hydrotropic agent," which he defined as a metallic salt of organic acid whose relatively high concentration in water can improve the aqueous solubility of organic compounds that are just poorly soluble in water. It is believed that salts that improve solubility "salt in" the solute, whereas salts that reduce solubility "salt out" the solution.**(6)**

Hydrotropic solubilization has been employed to enhance the aqueous solubility of several poorly water-soluble drug **(7-16)**

Mixed hydrotropic solubilization has been employed to enhance the aqueous solubility of several poorly water-soluble drug.**(17-29)**

Mixed solvency concept (30-32)

Dr. R.K. Maheshwari proposed the mixed solvency idea in 2009. Solvents are any substances that exist in a liquid state at room temperature. There is no such solvent as a universal solvent. Whatever name we provide a solvent, it is a good solvent for a few solutes but a bad solvent for others. Dr. R.K. Maheshwari's mixed solvency concept says that everything within the universe possesses solubilizing power, whether it's a gas, a liquid, or a solid. For a few solutes, each substance (solubilizer) could be a good solubilizer, except for others, it's a bad solubilizer. Dissolution of a solute in a solvent includes hydrogen bonding and weak van der Waals forces between molecules of solute and molecules of solvent. Any matter that exists in a liquid state at room temperature is known as a solvent. Each liquid (solvent) has good solubilizing control for a few solutes and bad solubilizing control for other solutes. Almost 35% of drugs are water-soluble and approximately 65% of drugs are water-insoluble. This implies water may be a good solvent for a few solutes (e.g. for 35% drugs) and a bad solvent for other solutes (e.g. for 65% drugs). In this way, we are able to say that water has good solubilizing power for a few solutes and bad solubilizing power for other solutes. Similarly, each matter (fluid, gas, or solid) is known as a solubilizer within the mixed solvency concept. Molecules of all solids (in liquid state) and gases (in liquid state) also have good solubilizing power for a few solutes and bad solubilizing power for other solutes..

Solid as solvent

The molecules of a solid may come in the liquid state in three ways:

A. By melting

B. By dissolution in a solvent

C. By eutectic formation.

Solubility (33-35)

- Solubility is defined in qualitative terms as the concentration of solute in a saturated solution at a certain temperature, and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. Solubility may be expressed as part, percentage, molarity, molality, or volume fraction.

Solubility is the quality or property of being soluble or solvable in general. The ability of a substance (referred to as a solute) to dissolve in a solvent Methods of Solubility Enhancement: Classical and highly employed approaches to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs, especially BCS Class II drugs, involve the solubilization by application of principles like pH adjustment, cosolvency, microemulsification, self-emulsification, micelles, liposomes, and emulsions. Each method deals with some merits and demerits. Hence, the decision of the method is a crucial step in the formulation process.

- Surfactants: The conventional approach to solubilizing a poorly soluble substance is to reduce the interfacial tension between the surface of the solute and the solvent for better wetting and salvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)-poly (propylene oxide) like Poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide), etc are very successful as excipient and carrier for dissolution enhancement. Amphiphilic surfactants improve drug solubility by lowering surface tension between the drug and the solvent, improving wetting characteristics, and increasing micellar solubility 10.

- pH adjustments: Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase the water solubility of ionizable compounds. As per the /pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug. The change in the ionic milieu can also result to in situ salt formation. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract.
- Salt formation: Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Of approximately 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form 12. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts 13. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion.

  Several reviews have outlined general strategies and considerations for salt selection. For the salt formation drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows:
  - There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
  - Counter ion should decrease crystal lattice forces.
  - It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.
  - This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.

- Colsolvents: Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. For example, Procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d-α- tocopherol (vitamin E) and oleic acid.

  Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil.
- Polymeric Alteration: Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

- Particle Size Reduction: Micronization or nanonization is one of the most potential approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level 18. Particle size is a critical parameter which should be strictly controlled during the preformulation studies of any formulation. Although the reduction in the particle size is a successful way to enhance the solubility, if uncontrolled and un-optimized, it can lead to re-crystallization and re-aggregation of drug on storage. Hence a thorough study on particle size and physical stability should be done.
- Size reduction to submicron range is not possible by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling high-pressure homogenization, solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS) is referred to as "solubility". A solid, liquid, or gaseous substance can be the solute. The solute's solubility is influenced by its physical and chemical properties. Temperature, pressure, the pH of the solution, and the properties of the solvent all are variables that impact solubility.

MATERIAL AND METHOD:

Phenol, PEG 4000, PEG 6000, BHA Methyl nicotinate, Thymol, Lignocaine HCl, Aspirin, Diclofenac sodium, Glyceryl mono stearate, Ondansetron HCl, Glimepiride, Benzoic acid, Stearic acid, Urea, Sodium salicylate, Sodium oleate, BHT, BHA, Sorbic acid, Salicyclic Acid, L-arginine were provided by Shri G.S. Institute of Technology & Science, Indore.

Method: 1 gm of phenol was taken in a test tube. The test tube was immersed in hot water to melt phenol. Then, 100mg of lignocaine HCl was added, and then the test tube was shaken in the melted condition of phenol. Since a clear solution was obtained, the test tube was kept undisturbed at room temperature. The next day, it was observed that the solution was clear. This means that eutectic liquid can be created using a 1:0.1 or 10:1 ratio (Table 2). Then, again, 100mg of lignocaine HCl was added, the test tube was shaken, and a clear solution was obtained. Then again, this liquid was kept undisturbed for 24 hours. After that, it was clear. This means eutectic liquid can be obtained using a 10:2 ratio of phenol and lignocaine HCl.It was found that.In the same way the eutectic liquid of phenol and lignocaine HCl can be made in 10:3, 10:4, 10:5, 10:6, 10:7, 10:8, 10:9.

The same procedure was used and found that, 1 gm of phenol and 1 gm of lignocaine HCl can also give eutectic liquid . After that, the study was discontinued.

A similar procedure was adopted for other combinations using PEG6000, a solid with a low melting point(58-63°C given in Table:03), PEG4000(melting point:53-58°C given in Table:04), Methyl nicotinate (melting point: 38.5-43°C given in Table:05), Thymol (melting point: 49-51°C given in Table:06), and BHA(melting point: 48-55°C given in Table:07).

Table 1: The reported melting ranges of compounds:

S. no.	Compound	Melting range (℃)
1.	Lignocaine HCl	66-68
2.	Aspirin	132-135
3.	Diclofenac sodium	279-289
4.	Ondansetron HCl	178-180
5.	Phenol	40.5-41
6.	Glyceryl mono stearate	50-55
7.	Benzoic acid	121-123
8.	Stearic acid	69.3-70
9.	Urea	133-135
10.	Sodium salicylate	200-213
11.	Sodium oleate	232-235
12.	BHT	69-73
13.	Sorbic acid	134.5-135
14.	Salicyclic acid	157-159
15.	BHA	48-55
16.	PEG 6000	58-63
17.	PEG 4000	53-58
18.	L-arginine	230-244
19.	Methyl nicotinamate	38.5-43
20.	L-lysine	215-224.5
21.	Vanillin	81-83
22.	Thymol	49-51
23.	Niacinamide	128-130
24.	Caffeine	227-228
25.	Camphor	175-179.7
26.	Menthol	36-38
27.	Glimepiride	205-207

Table 2: Trials for eutectic mixture formation using phenol as solid with a low melting range.

S.no.	Solid with low melting range(1g)	Compound	Quantity	Observation
1.	Phenol	Lignocaine HCl	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution

			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution
2.	Phenol	Aspirin	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Not Dissolved
3.	Phenol	Diclofenac sodium	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
4.	Phenol	Glyceryl mono stearate	100mg	Insoluble
5.	Phenol	Ondansetron HCl	100mg	Insoluble
6.	Phenol	Glimepiride	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution
7.	Phenol	Benzoic acid	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
8.	Phenol	Stearic acid (Melted form)	100mg	Clear solution After rest- Gel formation
9.	Phenol	Urea	100mg	Insoluble
10.	Phenol	Sodium salicylate	100mg	Insoluble
11.	Phenol	Sodium oleate	100mg	Insoluble
12.	Phenol	BHT	100mg	Clear solution
			200mg	Clear solution
13.	Phenol	Sorbic acid	100mg	Clear solution After rest -crystallization
			200mg	Insoluble
14.	Phenol	Salicylic acid	100mg	Insoluble
15.	Phenol	BHA	100mg	Clear solution
			200mg	Clear solution

			300mg	Clear solution
			400mg	Insoluble
16.	Phenol	Salicylic acid + BHA (Heat)	100mg +100g (1:1)	Clear solution
17.	Phenol	Sorbic acid + BHA (Heat)	100mg + 100mg (1:1)	Clear solution After rest – Gel formation
18.	Phenol	Stearic acid + BHA (Heat)	100mg + 100mg (1:1)	Gel formation
		Stearic acid + BHT (Heat)	100mg + 100mg (1:1)	Gel formation
19.	Phenol	Urea + BHT (Heat)	100mg + 100mg (1:1)	Gel Formation
20.	Phenol	Sorbic acid + BHA + Urea	100mg + 100mg + 100mg (1:1:1)	Clear solution by heat
21.	Phenol	Urea + BHA	200mg + 100mg (2:1)	Clear solution by Heat After rest – Gel Formation
22.	Phenol	Sorbic acid + BHA + Urea	100mg + 100mg + 100mg (1:1:1)	Clear solution
23.	Phenol	Urea + BHA + BHT	200mg + 100mg + 100mg (2:1:1)	Clear solution
24.	Phenol	Sorbic acid + BHA + Urea	100mg + 200mg + 100mg (1:2:1)	Clear solution
25.	Phenol	Urea +BHA + BHT	200mg + 200mg + 100mg (2:2:1)	Clear solution
26.	Phenol	Salicylic acid + BHA + BHT	100mg +200mg + 100mg (1:2:1)	Insoluble
27.	Phenol	Benzoic acid	100mg	Clear solution

			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
28.	Phenol	Stearic acid (Melted form)	100mg	Clear solution After rest- Gel formation
29.	Phenol	Urea	100mg	Insoluble
30.	Phenol	Sodium salicylate	100mg	Insoluble
31.	Phenol	Sodium oleate	100mg	Insoluble
32.	Phenol	BHT	100mg	Clear solution
			200mg	Clear solution
33.	Phenol	Sorbic acid	100mg	Clear solution After rest crystallization
			200mg	Insoluble
34.	Phenol	Salicylic acid	100mg	Insoluble
35.	Phenol	BHA	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Insoluble
36.	Phenol	Salicylic acid + BHA (Heat)	100mg +100g (1:1)	Clear solution

Table 3: Trials for eutectic mixture formation using PEG6000 as solid with a low melting range.

S. no.	Solid with low melting range(1g)	Compound	Quantity	Solubility status
1.	PEG6000 (100mg)	BHT	100mg	Clear solution
2.	PEG6000 (100mg)	Sorbic acid	100mg	Insoluble
3.	PEG6000 (100mg)	Glimepiride	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Insoluble

Table 4: Trials for eutectic mixture formation using PEG4000 as solid with a low melting range.

S.no.	Solid with low melting range(1g)	Compound	Quantity	Stability Status
1.	PEG4000	BHA	100mg	Clear solution by heat then solidified
			200mg	Clear solution by heat then solidified
2.	PEG4000	Sorbic acid	100mg	Clear solution by Heat then solidified
			200mg	Insoluble
3.	PEG4000	Benzoic acid	100mg	Clear solution by heat then solidified
			200mg	Insoluble
4.	PEG4000	Sodium salicylate	100mg	Insoluble
5.	PEG4000	BHT	100mg	Clear solution by heat then solidified
			200mg	Clear solution by heat then solidified
6.	PEG4000	Sodium oleate	100mg	Insoluble
7.	PEG 4000	Sodium salicylate + BHT	100mg + 100mg (1:1)	Insoluble
8.	PEG4000	L- arginine	100mg	Turbid
9.	PEG4000	BHA + BHT	100mg + 100mg (1:1)	Clear solution by heat then solidified
10.	PEG4000	Urea	100mg	Insoluble
11.	PEG4000	Urea + BHA	100mg + 100mg (1:1)	Insoluble
12.	PEG4000	Sorbic acid + BHA	200mg + 100mg (2:1)	Insoluble
13.	PEG4000	Benzoic acid + BHT	200mg + 100mg (2:1)	Insoluble

Table 5: Trials for eutectic mixture formation using methyl nicotinate as solid with a low melting range.

S. no.	Solid with low melting range(1g)	Compound	Quantity	Observation
1.	Methyl Nicotinate	BHT	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution
2.	Methyl Nicotinate	Sorbic acid	100mg	Clear solution then solidified
			200mg	Clear solution
			300mg	Clear solution
			400mg	Insoluble
3.	Methyl Nicotinate	Sodium oleate	100mg	Insoluble
4.	Methyl Nicotinate	L- arginine	100mg	Insoluble
5.	Methyl Nicotinate	Sodium oleate	100mg	Insoluble
6.	Methyl Nicotinate	L- lysine	100mg	Insoluble
7.	Methyl Nicotinate	Benzoic acid	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			1000mg	Clear solution
8.	Methyl Nicotinate	Vanillin	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution

			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution
9.	Methyl Nicotinate	BHA	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution

Table 6: Trials for eutectic mixture formation using thymol as solid with a low melting range.

S. no.	Solid with low melting range(1g)	Compound	Quantity	Observation
1.	Thymol	Urea	100mg	Insoluble
2.	Thymol(1gm)	BHA	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
3.	Thymol	Benzoic acid	100mg	Clear solution
4.	Thymol	BHT	100mg	Clear solution
5.	Thymol	Sodium oleate	100mg	Insoluble
6.	Thymol	Sorbic acid	100mg	Insoluble
7.	Thymol	Benzoic acid	100mg	Clear solution
			200mg	Insoluble

Table 7: Trials for eutectic mixture formation using BHA as solid with a low melting range.

S. no.	Solid with low melting range(1g)	Compound	Quantity	Observation
1.	BHA	BHT	100mg	Clear solution
			200mg	Clear solution
			300mg	Clear solution
			400mg	Clear solution
			500mg	Clear solution
			600mg	Clear solution
			700mg	Clear solution
			800mg	Clear solution
			900mg	Clear solution
			1000mg	Clear solution
2.	BHA	Sorbic acid	100mg	Insoluble
3.	BHA	Urea	100mg	Insoluble
4.	BHA	Sodium oleate	100mg	Insoluble
5.	BHA	L- lysine	100mg	Insoluble
6.	BHA	Niacinamide	100mg	Clear solution by heat then solidified
			200mg	Clear solution by heat then solidified
			300mg	Clear solution by heat then solidified
			400mg	Clear solution by heat then solidified
			500mg	Clear solution by heat then solidified
			600mg	Clear solution by heat then solidified
			700mg	Clear solution by heat then solidified
			800mg	Clear solution by heat then solidified
			900mg	Clear solution by heat then solidified
			1000mg	Clear solution by heat then solidified
7.	BHA	Caffeine	100mg	Clear solution by heat
			200mg	Clear solution by heat
			300mg	Clear solution by heat

			400mg	Clear solution by heat
			500mg	Clear solution by heat
			600mg	Clear solution by heat
			700mg	Clear solution by heat
			800mg	Clear solution by heat
			900mg	Clear solution by heat
			1000mg	Clear solution by heat
8.	BHA	Camphor	100mg	Clear solution by heat
			200mg	Clear solution by heat
			300mg	Clear solution by heat
			400mg	Clear solution by heat
			500mg	Clear solution by heat
			600mg	Clear solution by heat
			700mg	Clear solution by heat
			800mg	Clear solution by heat
			900mg	Clear solution by heat
			1000mg	Clear solution by heat
9.	BHA	Stearic acid	100mg	Clear solution by heat then solidified
			200mg	Clear solution by heat then solidified
			300mg	Clear solution by heat then solidified
			400mg	Clear solution by heat then solidified
			500mg	Clear solution by heat then solidified
			600mg	Clear solution by heat then solidified
			700mg	Clear solution by heat then solidified
			800mg	Clear solution by heat then solidified
			900mg	Clear solution by heat then solidified
			1000mg	Clear solution by heat then solidified
10.	BHA	Menthol	100mg	Clear Solution
			200mg	Clear Solution
			300mg	Clear Solution
			400mg	Clear Solution

			500mg	Clear Solution
			600mg	Clear Solution
			700mg	Clear Solution
			800mg	Clear Solution
			900mg	Clear Solution
			1000mg	Clear Solution
11.	BHA	Thymol	100mg	Clear Solution
			200mg	Clear Solution
			300mg	Clear Solution
			400mg	Clear Solution
			500mg	Clear Solution
			600mg	Clear Solution
			700mg	Clear Solution
			800mg	Clear Solution
			900mg	Clear Solution
			1000mg	Clear Solution

Table 8 : Composition of eutectic mixtures with a low proportion of compounds with higher melting range

S no.	Solid with low melting range(1g)	Compound	Result
1.	Phenol	Lignocaine HCl (100mg)	Formation of eutectic liquid
2.	Phenol	Aspirin (100mg)	Formation of eutectic liquid
3.	Phenol	Diclofenac sodium (100mg)	Formation of eutectic liquid
4.	Phenol	Glimeperide (100mg)	Formation of eutectic liquid
5.	Phenol	Benzoic acid (100mg)	Formation of eutectic liquid
6.	Phenol	BHA (100mg)	Formation of eutectic liquid
7.	Phenol	BHT (100mg)	Formation of eutectic liquid
8.	Phenol	Sorbic acid (100mg)	Formation of eutectic liquid
9.	Phenol	BHA (100mg)	Formation of eutectic liquid
10.	Phenol	Stearic acid (100mg)	Formation of eutectic liquid
11.	Phenol	Salicylic acid (100mg) + BHA(100mg) (Heat)	Formation of eutectic liquid
12.	Phenol	Sorbic acid (100mg) + BHA (100mg) (Heat)	Formation of eutectic liquid
13.	Phenol	Sorbic acid (100mg) + BHA (100mg) + Urea (100mg) (Heat)	Formation of eutectic liquid
14.	Phenol	Urea (200mg) + BHA (100mg)	Formation of eutectic liquid
15.	Phenol	Urea (200mg) + BHA (100mg) + BHT (100mg)	Formation of eutectic liquid

16.	Phenol	Sorbic acid (100mg) + BHA (200mg) + Urea (100mg)	Formation of eutectic liquid
17.	Phenol	Urea (200mg) + BHA (200mg) + BHT (100mg)	Formation of eutectic liquid
18.	Phenol	Salicylic acid (200mg) + BHA (200mg) + BHT (100mg)	Formation of eutectic liquid
19.	PEG6000	Glimepiride (100mg)	Formation of eutectic liquid
20.	PEG6000	BHT (100mg)	Formation of eutectic liquid
21.	PEG4000	BHA (100mg)	Formation of eutectic liquid
22.	PEG4000	Sorbic acid (100mg)	Formation of eutectic liquid
23.	PEG4000	Benzoic acid (100mg)	Formation of eutectic liquid
24.	PEG4000	BHT (100mg)	Formation of eutectic liquid
25.	PEG4000	BHA (100mg) + BHT (100mg)	Formation of eutectic liquid
26.	Methyl nicotinate	BHT (100mg)	Formation of eutectic liquid
27.	Methyl nicotinate	Sorbic acid (100mg)	Formation of eutectic liquid
28.	Methyl nicotinate	Benzoic acid (100mg)	Formation of eutectic liquid
29.	Methyl nicotinate	Vanillin (100mg)	Formation of eutectic liquid
30.	Methyl nicotinate	BHA (100mg)	Formation of eutectic liquid
31.	Thymol	BHA (100mg)	Formation of eutectic liquid
32.	Thymol	Benzoic acid (100mg)	Formation of eutectic liquid
33.	Thymol	BHT (100mg)	Formation of eutectic liquid
34.	Thymol	Benzoic acid (100mg)	Formation of eutectic liquid
35.	BHA	BHT (100mg)	Formation of eutectic liquid
36.	BHA	Niacinamide (100mg)	Formation of eutectic liquid
37.	BHA	Camphor (100mg)	Formation of eutectic liquid
38.	BHA	Stearic acid (100mg)	Formation of eutectic liquid
39.	BHA	Menthol (100mg)	Formation of eutectic liquid
40.	BHA	Thymol (100mg)	Formation of eutectic liquid

RESULT & DISCUSSION:

In the present research work various eutectic mixtures were prepared by employing two or more than two compounds in different ratios. Some blend combinations resulted in stable eutectic mixtures while some turned out to be unstable. The eutectic mixtures were formed by hit & trial method, as a result, mixing of some compounds resulted in a clear solution, and some get solidified after some time. In Table-8 illustrations of some eutectic mixtures created with a minimum concentration of compounds are given.

CONCLUSION:

Eutectic liquids may play a vital role in various operations like analysis of drug formulations, extraction of active constituents from herbal sources, synthesis of new compounds, and formulations of pharmaceutical dosage forms, including NDDS. As is evident from the present research work, innumerable eutectic liquids can be prepared by the use of several low-melting solids . At least one compound should have a low melting ranges. The melting range should

be close to room temperature. For example, in this research work, Lignocaine HCl (M.P.- 66ºC-68 ºC), Aspirin (M.P.-132 ºC -135 ºC), Diclofenac sodium (M.P.-278 ºC -289 ºC) phenol (M.P.-40.5 ºC -41 ºC), PEG 6000 (M.P.-58 ºC -63 ºC) and have been selected. The melting ranges of these compounds are close to room temperature. Thus, it may be concluded that this research work will be a boon for the development of a large number of eutectic forming combinations in the future .

REFERENCE:

1. Balakrishnan I JN, SV, Debosmita Datta. A Brief Review On Eutectic Mixture And Its Role In Pharmaceutical Field. 2020;3.

2. Bi M, Hwang S-J, Morris KR. Mechanism Of Eutectic Formation Upon Compaction And Its Effects On Tablet Properties. Thermochimica Acta. 2003;404(1):213-26.

3. Hoang Pham UG. Pharmaceutical Applications Of Eutectic Mixtures. Journal Of Developing Drugs. 2013;02(03).

4. Zhang Q, De Oliveira Vigier K, Royer S, Jérôme F. Deep Eutectic Solvents: Syntheses, Properties and Applications. Chemical Society Reviews. 2012;41(21):7108-46.

5. Singh A, Maheshwari R. "Solid As Solvent"-Novel Spectrophotometric Analytical Technique For Quantitative Estimation Of Piroxicam In Tablets Using Solids (Eutectic Liquid Of Phenol And Lignocaine Hydrochloride) As Solubilizing Agents (Mixed Solvency Concept). 2015.

6. Kapadiya N, Singhvi, I., Mehta, K., Karwani, G., Sen, D.J. , . "Hydrotropy: A Promising Tool For Solubility Enhancement." International Journal Of Drug Development And Research,. 2011;3(2):26-33.

7. Jain N, Jain R, Jain A, Pandey SP, Jain DK. Spectrophotometric Method Development And Validation For Quantitative Estimation Of Amlodipine Besylate In Bulk Drug And Their Dosage Forms By Using Hydrotropic Agent. Jorunal Eurasian Journal Of Analytical Chemistry. 2010;5(3):212-7.

8. Maheshwari R, Arif D, Mittal P, Manchandani P, Indurkhya A, Jawade S. A Novel Method For Quantitative Determination Of Aceclofenac In Bulk Drug And Tablets Using Ibuprofen Sodium As A Hydrotropic Solubilizing Agent. J J Appl Chem Resh. 2008;5:63-8.

9. Maheshwari R, Pandey S, Ramchandani U, Gupta HM. Analysis Of Frusemide By Application Of Hydrotropic Solubilization Phenomenon In Solid Dosage Form. Asian Journal Of Chemistry. 2008;20(1):277.

10. Maheshwari R, Joshi, G., Gehlot, S., Mahajan, S.C. Novel Application Of Hydrotropy In Thin Layer Chromatography. The Indian Pharmacist. 2010;8:57-9.

11. Maheshwari RK, Pandey, S., Lovlekar, A. ,Chavda, V., Ajmera, A., Gupta, H. M. Novel Application Of Hydrotropic Solubilization In The Spectrophotometric Analysis Of Cephalexin In Solid Dosage Form. Asian Journal Of Chemistry. 2006;18:1451-4.

12. Mangal A, Bhadoriya, S., Verma, A., Mishra, K. Novel Application Hydrotropic Solubilization Phenomenon In The Thin Layer Chromatrography Analysis Of Omeprazole. Journal Of Current Pharmaceutical Research. 2011;8(1):15-6.

13. Shukla T, Khare P, Pandey S. Role Of Hydrotropic Salt Solutions In Pharmaceutical Research: Past Present And Future. International Journal Of Pharmacy.Pharmaceutical Sciences. 2014;6(4):3-6.

15. Hamza YEP, A. N. . Enhanced Solubility Of Paracetamol By Various Hydrotropic Agents. Drug Delivery Indian Pharmaceutics. 1985(11):1577-96.

16. Jayronia SY, K; Sharma, B.; Jain, S.; Maheshwari, R. K. Hydrotropy: A Novel Approach In Estimation Of Poorly Aqueous Soluble Drugs By TLC. International Journal Of Pharmaceutical Sciences. 2013;5:176-8.

17. Maheshwari RK, Jagwani, Y. “Mixed Hydrotropy: Novel Science Of Solubility Enhancement.”. Indian Journal Of Pharmaceutical Sciences. 2011;6:179-83.

18. Maheshwari RK, Sharma, S., Rai, N., Rajput, M. “Simple Titrimetric Method To Estimate Ketoprofen In Bulk Using Mixed Hydrotropy.”. Journal Of Pharmacy Research. 2010;3(3):442-3.

19. Shrivastav R, Khare, A., Agrawal, S., Patel, S.,. “New Titrimetric Estimation Of Aceclofenac Tablets Using Mixed Hydrotropy.”. International Journal Of Pharmaceutical Sciences Review And Research,. 2011;11(140-141).

20. Maheshwari RK, Pathak, S., Sahu, P. “Ecofriendly Application Of Mixed Hydrotropy For Titrimetric Analysis Of Ibuprofen Tablets.”. International Journal Of Science And Research,. 2021;10(5):954-6.

21. Nair V, Rajput, M.S., . “A Simple Spectrophotometric Estimation Of Ketoprofen In Tablets Using Mixed Hydrotropy.” Der Pharma Chemica,. 2010; 2(2):267-71.

22. Maheshwari RK, Rathore, A., Agrawal, A. “New Spectrophotometric Method To Determine Ketoprofen In Tablet Dosage Form By Applying Mixed Hydrotropy.”. International Journal Of Chemical And Analytical Sciences. 2010;1:62-3.

23. Maheshwari RK, Rajput, M.S., Sharma, S., Nair, V. “New Spectrophotometric Determination Of Hydrochlorothiazide In Tablets Using Mixed Hydrotropic Solubilization Technique.”. Der Pharmacia Letter. 2010;2(1):70-4.

24. Sanap DD, Sisodiya, A.M., Patil, S.H., Janjale, M.V. “Novel And Validated Spectrophotometric Determination Of Budesonide From Bulk And Tablets Using Mixed Hydrotropic Solubilization Technique.” International Journal Of Pharmaceutical Sciences And Research. 2011;2(9):2419-23.

25. Shrivastava R, Jain, R., Patel, S. “Spectrophotometric Analysis Of Gatifloxacin Tablets Using Mixed Hydrotrophy.”. International Journal Of Pharmaceutical Sciences And Research, . 2011;2(10):2709-11.

26. Kadam SR, Janjale, M.V., Akole, S.B., Bhosle, S.S.,. “Application Of Mixed Hydrotropic Solubilization Technique For Simultaneous Spectrophotometric Estimation Of Metronidazole And Miconazole Nitrate From Different Pharmaceutical Dosage Forms.”. International Journal Of Pharmaceutical & Biological Archives,. 2012;3(2):383-90.

27. Jain R, Jain, N., Maheshwari, R.K., Jain, S.K. . “Quantitative Estimation Of Levofloxacin And Ornidazole By Uv Spectrophotometer: A Mixed Hydrotropy Solubilization Approach.”. International Journal Of Pharmaceutical Sciences And Research. 2013;4:3073-9.

28. Jain R, Jain, N., Jain, D.K., Patel, V.K., Rajak, H, Jain, S.K. “Novel Uv Spectrophotometer Methods For Quantitative Estimation Of Metronidazole And Furazolidone Using Mixed Hydrotropy Solubilization.”. Arabian Journal Of Chemistry, . 2013;10(1):151-6.

29. Remi SL, Varkey, J.,. “An Ecofriendly Novel Spectrophotometric Estimation And Validation Of Paliperidone In Bulk Drugs And Their Dosage Forms By Mixed Hydrotropic Solubilisation Method.” Asian Journal Of Pharmaceutical And Health Sciences, . 2018;8(4):1996-2001.

30. Ludhiani S, Maheshwari R.K. . A Review Article: Mixed Solvency Concept In Formulation And Extraction. International Jornal Of Pharmacy And Pharmaceutical Research 2021;21:75-110.

31. Solanki SS, Soni LK, Maheshwari RK. Study On Mixed Solvency Concept In Formulation Development Of Aqueous Injection Of Poorly Water Soluble Drug. Journal Of Pharmaceutics. 2013;2013:678132.

32. Maheshwari N, Baghel J, Mulani P, Padria, Jain AS, Maheshwari RK. "Eco-friendly Extraction Using Solids" - A Novel Application Of Mixed Solvency Concept. Journal Of Drug Delivery And Therapeutics. 2019;9(2):244-9.

33. Abranches OD, Benfica J, Soares B, Duaso A, Shimizu S, Pinho S. Unveiling The Mechanism Of Hydrotropy: Evidence For Water-mediated Aggregation Of Hydrotropes Around The Solute. Chem Community. 2020;56(52):7143-6.

34. Vemula L, V., Lingala, L., Srikanth. Solubility Enhancement Techniques. International Journal Of Pharmaceutical Sciences Review. 2010;5(1):41-51.yyg

35. Thorat YS, Gonjari ID, Hosmani. International Journal Of Pharmaceutcial Sciences And Research. Solubility Enhancement Techniques: A Review On Conventional And Novel Approaches. 2011;2(10):2501.